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EXAMINER
GREEN, L

18N1/0712

ART UNIT PAPER NUMBER

TOWNSEND AND TOWNSEND
STEUART STREET TOWER
ONE MARKET PLAZA
SAN FRANCISCO, CA 94105

1802

DATE MAILED: 07/12/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 6-15-94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-848. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> |

Part II SUMMARY OF ACTION

1. ☒ Claims 105, 107-115, 117-120 are pending in the application.

Of the above, claims are withdrawn from consideration.

2. ☐ Claims have been cancelled.
3. ☐ Claims are allowed.
4. ☒ Claims 105, 107-115, 117-120 are rejected.
5. ☐ Claims are objected to.
6. ☐ Claims are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-848).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. ; filed on
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1835 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

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This action is responsive to the amendment after final filed 6-15-94, which has been entered.

The finality of the office action mailed 2-22-94 is withdrawn, and prosecution on the merits has been reopened.

Claims 105, 107-115 and 117-120 are pending.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure.

The claims are drawn to substrates with 100 or more groups of oligonucleotides immobilized on the surface at predefined regions. In Science, Volume 253, issued September 27, 1991, Fodor states that at the time of that article (which is after the effective filing date of the instant application) '"We have just completed moving up to 65,000" sites in a 1.28-cm-square array'. In view of this statement, and that the instant disclosure does not teach the production of a substrate comprising up to 10^6 or more different groups of oligonucleotides, it would require an undue amount of experimentation by one skilled in the art to produce such substrates without guidance from Applicants that the

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method disclosed in the instant application is capable of producing such substrates.

Claims 105, 107-115 and 117-120 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 105, 107, 108 and 109 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited substrates comprising groups of oligonucleotides in which the oligonucleotides are covalently attached to the support. See M.P.E.P. §§ 706.03(n) and 706.03(z).

These claims read on oligonucleotides which are either passively adsorbed or covalently attached to the substrate. The only type of substrate for which Applicants can achieve the claimed resolution, i.e. such as an area of $100\mu\text{m}^2$, is one in which the oligonucleotides are covalently coupled to the substrate, and it would require an undue amount of experimentation by one skilled in the art to achieve such resolution in which the oligonucleotides are adsorbed to the substrate without guidance from Applicants on means of producing such substrates.

Claims 105, 109-115 and 117-120 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claims 105, 110 and 117 are indefinite in the use of the phrase "predefined regions" as it is unclear how the regions are "predefined".

Claim 105 is indefinite, as it is unclear how the 100 or more groups of oligonucleotide molecules are related to the at least two predefined regions.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --
(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim 105 is rejected under 35 U.S.C. § 102(e) as being anticipated by Drmanac et al. (US 5,202,231).

Drmanac et al. teach application of DNA subclones on filters by a robotic arm, in which the micropipets are positioned to each other of a distance to 1mm., and a quantity of DNA suitable for 10,000 subclones is applied to the filter simultaneously, and the procedure is repeated with the same 10,000 subclones as many times as necessary. These "dot" are then used for hybridization with oligonucleotide probes of known sequence (column 7, line 53-column 8, line 7). This reads on a substrate comprising oligonucleotides of known sequence due to the open claim

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language, comprising, and as 1mm dots correspond to an area of 0.008cm².

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 105, 109-115, 117, 119 and 120 are rejected under 35 U.S.C. § 103 as being unpatentable over Khrapko et al.

Khrapko et al. teach a DNA sequencing method based on the hybridization of a DNA fragment to be sequenced with the complete set of fixed length oligonucleotides (e.g. 4⁸=65,536 possible 8-mers) immobilized individually as dots of a 2-D matrix. This

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reference specifically teaches immobilization of oligonucleotides as 2mm dots on a glass plate covered with a 10 μ m layer of activated polyacrylamide. 2mm dots correspond to an area of 0.03cm², which reads on an area of about 0.01cm². In addition, in view of the teach that a set of 65,536 possible 8-mers is required for the sequencing, it would have been obvious to immobilize any number of dots on the glass plate. The substrate obtained would be the same no matter what method was used to put the oligonucleotides on the surface.

Claims 105, 107-115 and 117-120 are rejected under 35 U.S.C. § 103 as being unpatentable over Southern et al. in view of, if required, Lowe et al. (US 4,562,157), Clark et al. (US 4,728,591), or Schnur et al. (US 5,079,600).

Southern et al. teach an apparatus for analyzing a polynucleotide sequence (WO 89/10977), comprising a support and attached to a surface thereof an array of the whole or a chosen part of a complete set of oligonucleotides of chosen lengths. This reference teaches a method of producing the support, in which the oligonucleotides are synthesized in situ by laying down the precursors for the for bases in a predetermined pattern, for which a pen plotter or other computer-controlled printing device could be adapted, or by masking areas with silicone rubber. This reference teaches that on a paper support, 100 microns would be a fairly comfortable limit, and on a smooth impermeable surface,

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such as glass, it may be possible to achieve a solution of around 10 microns (page 11, lines 10-29).

Lowe et al. teach the use of photolithographic processes to attach a biochemical ligand to a substrate, and teaches that it is possible to use a photoactivation technique to select minutely small areas, most suitably with the aid of a mask, and thereby successfully attach the biochemical ligand covalently in those areas only.

Clark et al. teach the lithographic production of arrays of nanometer biomolecular structures (e.g. column 2, lines 63-column 3, line 4; column 5, lines 55-column 6, line 30; column 10, lines 41-63).

Schnur et al. teach high resolution patterning on solid substrates, and teach creation of "spatially different areas of reactivity", and that polymeric materials can be involved (column 8, lines 27-41).

It would have been obvious to one of ordinary skill in the art to form a substrate having any desired number of oligonucleotides immobilized thereon as taught by Southern et al. because this reference teaches their use in sequencing of complex genomes, and teaches procedures which may be utilized for their manufacture, and teaches that on a glass substrate, a resolution of 10 microns would be possible. In addition, Lowe et al., Clark et al. and Schnur et al. are cited for teaching that other

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methods of immobilizing polymers such as biomolecules to minute areas, such as the photolithographic methods taught by Lowe and Clark et al., are known in the art, and Southern et al. provide motivation for adapting such methods to the immobilization of oligonucleotides. It would have also been obvious to use a linker to attach the oligonucleotides to the support because the use of linkers is well known and routine in the art, and the use of such a linker would prevent steric hindrance with the substrate.

Applicant's arguments have been considered but are deemed to be moot in view of the new grounds of rejection.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Mirzabekov (TIBTECH) is cited as a review of matrices of immobilized DNA or oligonucleotides.

Southern et al. (Genomics) teach production of an oligonucleotide matrix using the silicone rubber masking technique disclosed in WO 89/10977.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora M. Green, Ph.D. whose telephone number is (703) 308-3999. The examiner can normally be reached M-F from 7:00am to 3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Esther Kepplinger, can be reached at (703)308-1219. The fax number for this group is (703)308-4227.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

LMG
7/5/94

A handwritten signature in cursive script, reading "Esther M. Kepplinger".

**ESTHER M. KEPPLINGER
SUPERVISORY PATENT EXAMINER
GROUP 1800**